Patent No. 6,333,021, issued to Schneider et al. ("Schneider"). Claims 73 and 74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Heathcoate et al., "A Pilot Study of the CY-1899 T-cell Vaccine in Subjects Chronically Infected With Hepatitis B Virus," *Hepatology 30*(2):531-536, 1999 ("Heathcoate"), in view of Tam and Vitiello.

Applicants respectfully submit that each of the obviousness rejections is improper because the Examiner has not established a *prima facie* case of obviousness, for the reasons already of record. However, applicants also submit that the evidence provided in the Declaration of Dr. Wu overcomes any *prima facie* assertion of obviousness. Specifically, the Declaration of Dr. Wu demonstrates that the results presented in the present application provide an effect that is greater than the additive effect of the hypothetical combination of the teachings of Vitiello and Tam. Further, neither Vitiello nor Tam provide any indication that a hypothetical combination thereof would produce synergic effects. Applicants therefore disagree with each of the rejections and submit that the claims are presently in condition for allowance.

A. Claims 1-16, 23, 54-60, 62, 63, and 65 are patentable over Vitiello and Tam

Claims 1-16, 23, 54-60, 62, 63, and 65 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Vitiello in view of Tam. The Examiner asserts that Vitiello teaches immunogen peptides comprising both T helper epitope derived from tetanus toxoid and a CTL epitope derived from HBV. The Examiner admits that Vitiello is silent as to incorporating a B cell epitope into the polypeptide. However, the Examiner asserts that Tam teaches a synthetic peptide containing T cell epitope and B cell epitopes from HBV. The Examiner asserts that each reference teaches that combining multiple epitopes of T helper, B cell and/or CTL epitopes can enhance the immunogenicity of a peptide immunogen, and therefore the results shown in the present specification are expected and not surprising. The Examiner concludes that based on Tam and Vitiello, one skilled in the art at the time of the invention would have been motivated to

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generate the claimed immunogen comprising T helper, CTL and B cell epitopes. Applicants respectfully disagree.

Because it is difficult to predict what epitope or combinations of epitopes will elicit a strong and effective immune response, before the present application it was not possible to predict that the combination recited in Claim 1 would elicit strong immunity. For example, none of the cited references, whether alone or in combination, teach or suggest that an immunogen comprising a Th cell epitope, a CTM epitope from HBV, and a B cell epitope from HBV covalently linked together by linking peptides consisting of 3-7 amino acid residues would elicit a strong immunity as demonstrated in the present application.

M.P.E.P. § 716.02(a) states that a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness. Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

As set forth in the Declaration of Dr. Wu, submitted herewith, the results set forth in the application as originally filed demonstrate that the combination of T helper, CTL and B cell epitopes had much greater effect than the additive effect (i.e. synergistic effect) compared to the combination of immunogens with T helper and CTL epitopes, and with T helper and B cell epitopes.

First, a combination of T helper, CTL and B cell epitopes in an immunogen resulted in a more than additive increased target killing rate by PBMCs compared to killing rates resulting from immunogens with different combinations of two epitopes. As described in Example 55 of the present application, PBMCs from patients with acute and chronic hepatitis demonstrated target cell lysis rates of 68.6% and 42.6%, respectively, after stimulation with an immunogen

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that incorporates T helper, CTL and B cell epitopes ("D1"). In stark contrast, similar PBMCs stimulated with immunogens incorporating only CTL and T helper epitopes ("D2") elicited target killing rates of 21.3% and 15.1%, respectively. Similarly, similar PBMCs stimulated with immunogens incorporating only T helper and B cell epitopes ("D3") elicited target killing rates of 5.3% and 4.3%, respectively. See Declaration of Dr. Wu, paragraph 6. Therefore, it is readily apparent that the target killing rate of PBMCs stimulated with immunogens incorporating T helper, CTL and B cell epitopes greatly exceeds the added killing rates of similar PBMCs stimulated with immunogens that incorporate only T helper and CTL epitopes, and immunogens that incorporate only T helper and B cell epitopes.

Second, stimulation with immunogens with a combination of T helper, CTL and B cell epitopes resulted in a more than additive increase in expression frequency of IFN-γ as compared to the stimulation with immunogens with different combinations of two epitopes. As described in Example 58 of the present application and in paragraph 7 of the Declaration of Dr. Wu, HBV transgenic mice were immunized with compounds D1, D2, or D3 (described above). Spleen lymphocytes were later extracted, re-stimulated in vitro, and the expression frequency of IFN-γ was measured. Mice stimulated with the D1 immunogen (incorporating T helper, CTL and B cell epitopes) produced 3660 secreting cells/10^6 PBMC. In stark contrast, mice stimulated with immunogen D2 (incorporating only CTL and T helper epitopes) produced 183 secreting cells/10^6 PBMC. Similarly, mice stimulated with immunogen D3 (incorporating only T helper and B cell epitopes) produced 3 secreting cells/10^6 PBMC. See Declaration of Dr. Wu, paragraph 7. Therefore, it is readily apparent that after stimulation with an immunogen incorporating T helper, CTL and B cell epitopes, the frequency of PBMCs secreting IFN-γ exceeds by over an order of magnitude the sum of results obtained from immunogens incorporating only T helper and CTL epitopes, and immunogens incorporating only T helper and B cell epitopes.

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Third, stimulation with immunogens with a combination of T helper, CTL and B cell epitopes resulted in a more than additive decrease in serum HBV surface antigen levels as compared to the stimulation with immunogens with different combinations of two epitopes. As described in Example 59 of the present application and in paragraph 8 of the Declaration of Dr. Wu, HBV transgenic mice were immunized with compounds D1, D2, or D3 (described above). Blood was drawn from the mice at various time points and the levels of serum HBV surface antigen were assayed. As described in paragraph 8 of the Declaration of Dr. Wu, the levels of HBV surface antigen in mice stimulated by the D1 immunogen decreased by more than 200 times in a manner of dose-dependence and time-dependence. In stark contrast, the levels of HBV surface antigen were not significantly altered upon stimulation of the D2 (incorporating only CTL and T helper epitopes) or D3 immunogens (incorporating only T helper and B cell epitopes). See Declaration of Dr. Wu, paragraph 8. Therefore, it is readily apparent that stimulation with immunogens incorporating T helper, CTL and B cell epitopes has a drastic reducing effect on the levels of serum HBV surface antigen compared to stimulation with immunogens incorporating only T helper and CTL epitopes, and immunogens incorporating only T helper and B cell epitopes.

Fourth, stimulation with immunogens with a combination of T helper, CTL and B cell epitopes resulted in a more than additive decrease in HBV replication as compared to the stimulation with immunogens with different combinations of two epitopes. As described in Example 60 of the present application and in paragraph 9 of the Declaration of Dr. Wu, the copy number of HBV DNA detected in all HBV transgenic mice stimulated by the D1 immunogen was greatly reduced to $<10^2$ copies/ml. In stark contrast, for mice stimulated by the D2 immunogen, the copy number was reduced to only 10^3-10^4 to copies/ml in 12 of 15 mice, and not reduced at all for 3/15 mice. For mice stimulated by the D3 immunogen, the copy number

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was not significantly reduced at all for all mice. Therefore, it is readily apparent that stimulation with immunogens incorporating T helper, CTL and B cell epitopes has a drastic reducing effect on the levels of HBV viral replication. The reduction was more than additive of the effects of similar stimulations with immunogens incorporating only T helper and CTL epitopes, and immunogens incorporating only T helper and B cell epitopes.

Fifth, consistent with the results described above, an immunogen with a combination of T helper, CTL and B cell epitopes caused a strong CTL response and reduction of virus load and serological transformation in tested humans. As described in paragraph 10 of the Declaration of Dr. Wu, the D1 immunogen was authorized to enter human clinical trials. The results of the trials indicate that D1 stimulation produced consistently strong CTL response (5-7% increase) and significant (2 log) reduction in serum HBV DNA levels. Further, in 5 of 10 subjects stimulation with D1 resulted in serological transformation and ultimately negative HbeAg. Immunogens D2 and D3 were not authorized for similar studies. These results indicate that immunogens that incorporate T helper, CTL and B cell epitopes perform similarly to their roles in mice as described above.

In consideration of the results set forth in the application as originally filed as described evidenced by the Declaration of Dr. Wu, it is demonstrated that immunogens incorporating T helper, CTL and B cell epitopes result in a significantly enhanced immune response as compared to immunogens incorporating only T helper and CTL epitopes, and immunogens incorporating only T helper and B cell epitopes. Moreover, it is demonstrated that the enhanced effect is greater than the additive effects obtained with the immunogens only T helper and CTL epitopes, and T helper and B cell epitopes. Further, there is no teaching in the Vitiello or Tam references that would remotely suggest that the combination of the references would result in a synergistic effect. In contrast, the teachings of Vitiello and Tam would only lead a person of ordinary skill

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in the art to have expected, at most, an additive effect of the combination of the immunogens taught therein. Therefore, a person of ordinary skill in the art could not have expected the enhanced results or significant, practical advantages as taught by the claimed invention.

B. Claims 64, 65, 71, and 72 are patentable over Vitiello and Tam in further view of Schneider

Claims 64, 65, 71, and 72 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Vitiello and Tam, and further in view of U.S. Patent No. 6,333,021, issued to Schneider et al. ("Schneider"). Claims 64, 65, 71, and 72 each depend from Claim 1. The deficiencies of the teaching of the Vitiello and Tam references noted above with regard to Claim 1 are not cured by the teaching of the Schneider reference. The Schneider reference describes microcapsules, methods of use and manufacture thereof, useful as delivery vehicles for therapeutically active agents to human or animal bodies. The Schneider reference does not teach or suggest an immunogen incorporating T helper, CTL and B cell epitopes.

Because the teachings of the cited references, alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention, the claimed invention is nonobvious and patentable over the cited references.

C. Claims 73 and 74 are patentable over Heathcoate in view of Tam and Vitiello

Claims 73 and 74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Heathcoate et al., "A Pilot Study of the CY-1899 T-cell Vaccine in Subjects Chronically Infected With Hepatitis B Virus," *Hepatology 30*(2):531-536, 1999 ("Heathcoate"), in view of Tam and Vitiello. Claims 73 and 74 are methods that incorporate the use of the compound of Claim 1. The Examiner characterizes the Heathcoate reference as teaching a method of inducing an immune response in HBV-infected patients comprising administering a peptide with T-helper and CTL epitopes. The Examiner admits that Heathcoate does not teach or suggest a vaccine

that also comprises a B cell epitope. The deficiencies of the teaching of the Heathcoate reference are not cured by the teachings of Vitiello and Tam references for the same reasons noted above with regard to Claim 1.

Because the teachings of the cited references, alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention, the claimed invention is nonobvious and patentable over the cited references.

CONCLUSION

In view of the foregoing remarks, supported by the Declaration of Dr. Wu, applicants respectfully submit that Claims 1-16, 23, 54-60, 62-65, and 71-74 are in condition for allowance. Reconsideration of the application and allowance of the pending claims are respectfully requested. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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